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14

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/837,235	04/18/2001	Christopher P. Marshall	9725-005	1399

7590 03/31/2004
Jane M. Love, Ph.D.
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EXAMINER

SAIDHA, TEKCHAND

ART UNIT	PAPER NUMBER
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1652

DATE MAILED: 03/31/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/837,235

Applicant(s)

MARSHALL ET AL.

Examiner

Tekchand Saidha

Art Unit

1652

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 4February 2004.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 10-13, 18-20 and 22-26 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 10-13, 18-20 and 22-26 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|---|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

Final Rejection

1. Applicants' Amendment filed February 4, 2004 has been entered. Claims 1-9, 14-17 and 21 have been cancelled.
2. Claims 10-13, 18-20 and 22-26 are pending and under consideration in this examination.
3. Applicant's arguments filed as per the amendment cited above have been fully considered but they are not deemed to be persuasive. The reasons are discussed following the rejection(s).
4. Any objection or rejection of record which is not expressly repeated in this Office Action has been overcome by Applicant's response and withdrawn.
5. ***Claim Rejections - 35 USC § 112*** (first paragraph)

Claims 10-13 & 22-26 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an isolated stabilized protein, comprising isolating a specific polypeptide, selecting one or more tyrosine residue pairs in a polypeptide chain, cross-linking the tyrosine residue pair(s) under defined conditions whereby the cross-linked protein retains at least one of its original function, does not reasonably provide enablement for any isolated protein comprising a di-tyrosine cross-link by wherein at least one tyrosine of a di-tyrosine cross-link originates from a point mutation. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Art Unit: 1652

Claims 10-13 & 22-26 are drawn to 'an isolated protein comprising at least one di-tyrosine cross-link', wherein at least one tyrosine of a di-tyrosine cross-link originates from a point mutation, wherein the protein is a hormone, a receptor, a growth factor, an enzyme or an antibody.

While recombinant and mutagenesis techniques are known, it is not routine or known in the art or enable in the instant specification to introduce a di-tyrosine cross-link wherein at least one tyrosine of a di-tyrosine cross-link originates from a point mutation without affecting the functionality of the protein in question. Genetic modification of the protein structure to introduce or substitute an amino acid with a tyrosine is well known (example – Brown et al. (1998) in a peptide chain, however, introducing such a cross-link between two tyrosine in a peptide chain by point mutation is not. Cross-linking of tyrosine residues has been achieved by chemical methods and under defined conditions such as in the presence of oxidants : oxone and monoperoxyphthalic acid (MMPP). However genetic expression of tyrosyl-tyrosyl cross-linked protein remains unknown and therefore claims to recombinantly produced cross-linked protein(s) or by point mutation, or compositions thereof are not enabled.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims. No specific examples are outlined in the specification that teach or provide guidance a protein structure or a method of obtaining such a cross-linked protein, wherein at least one tyrosine of a di-tyrosine cross-link originates from a point mutation, and wherein the protein is a hormone, a receptor, a growth factor, an

Art Unit: 1652

enzyme or an antibody. The scope of the claims encompass cross-linking any number of protein constructs which would include any hormone, any receptor, any growth factor, any enzyme or any antibody, many of which hitherto undiscovered. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of the production of recombinant cross-linking having the desired biological characteristics or function is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue in using the modified enzyme in the method claimed. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Applicants' Arguments :

Applicants argue that as per Examiner's assertion that genetic modification of a known protein [not any protein] is well known and that claim 10 is now directed to an isolated protein wherein at least one di-tyrosine cross-link is introduced by point mutation.

In response, it is pointed out that Applicants have no basis for 'point mutation' in their specification. Further, as pointed out in the rejection, genetic expression of tyrosyl-tyrosyl cross-linked protein remains unknown and therefore claims to recombinantly produced cross-linked protein(s) or that obtained by point mutation, or compositions thereof are not enabled.

Art Unit: 1652

6. Claim Rejections - 35 USC § 112 (second paragraph)

Claims 13, 20 & 22-26 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 13, lines 2, recites 'protein comprises an enzyme, an antibody or a fragment thereof'. The claim is indefinite because 'a protein comprises amino acids residues' and not an enzyme, an antibody or a fragment thereof. Amending the claim to recite "wherein a protein is an enzyme or an antibody" will overcome this rejection

Claim 20, lines 1-2, recites 'wherein cross-linking is catalyzed by a catalyst selected from the group consisting of polyhistidine, Gly-Gly-His, metalloporphyrin, a peroxidase or any combination thereof'. The claim is indefinite because it is unclear what cross-linking reaction is catalyzed by "polyhistidine, Gly-Gly-His, metalloporphyrin, or a peroxidase". Clarification is required.

Claims 22, line 3-4, recites 'protein comprises a hormone, a receptor, etc.,...'. The claim is definite for the same reason as given for claim 13. Amending the claim to recite "wherein a protein is a hormone oran antibody" will overcome this rejection.

Claims 23, lines 1-2, recites 'wherein the protein further comprises a pharmaceutical composition'. The claim is indefinite because 'a protein comprises amino acids residues' and can not comprise a pharmaceutical composition. Amending the claim to recite "a composition comprisinga protein, etc." will overcome this rejection. [Since, claims to a 'pharmaceutical composition' do not meet the enablement requirement (see rejection in prior Office Action), claims drawn to 'composition'

Art Unit: 1652

comprising specific cross-linked protein construct having a specific function' will overcome this rejection.

Claims 24-26 are included in the rejection for failing to correct the defect present in the base claim(s). All the 112-2nd paragraph rejections made here are in response to Applicants' amendment.

7. ***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

Claims 18-19 are rejected under 35 U.S.C. 102(b) as being anticipated by Aeschbach et al. (1976), BBA 439, 292-302 (AA – IDS). Aeschbach et al. teach a

Art Unit: 1652

method for formation of Dityrosine cross-links in proteins, the hormone insulin for example, by oxidation using hydrogen peroxide. The reference teaches all the claim limitations, is therefore anticipatory.

Applicants Arguments :

Applicants argue that claims as amended are not taught by Aeschbach et al. and 'do not include the limitation – at least one tyrosine of the di-tyrosine cross-link originates from a point mutation to tyrosine'.

In response, claims 18-19, do not include such a limitation, and therefore, the rejection for these claims have been retained.

8. Claims 10-13, 18-20 & 22 are rejected under 35 U.S.C. 102(b) as being anticipated by Brown et al. [Biochemistry, 1998, 37 : 4397-4406, **AD** - IDS]. Brown et al. teach protein-protein cross linking to be mediated by Ni(II) complex of the tripeptide gly-gly-his fusion protein, target being tyrosine, in the presence of oxidants such as oxone and monoperoxyphthalic acid (MMPP) and method of making the cross-linked peptide. Cross-linking has been achieved for small peptides, ecotin or GGH-ecotin cross-linked to a serine protease without loss of function. The cross-linking methodology allows for the protein cross-linking reagent to be encoded at the DNA level, thus circumventing the need for post-translational modification (see Abstract and Results and Discussion), even though the crossing linking is still oxidative. PCR-mutagenesis was performed to change ecotin Asp-137 to a tyrosine. The GGH-ecotin D137Y was subjected to same cross-linking conditions with no change in the binding affinity (see page 4402, column 2, 1st paragraph). All the claim limitations being taught, the reference anticipates the claims.

Applicants' Arguments :

Applicants argue that the reference does not disclose a di-tyrosine (DT) bonded protein that retains function.

Applicants are referred to page 4402, column 1 & column 2, lines 1-10, wherein the rationale for protein engineering is discussed, and based upon the results, it is suggested that residues can be changed with little or no effect on the binding affinity or the protein structure. This is indicative of the fact that the function of the protein is unaffected. Further, there is no negative teaching in the reference that suggests cross-linking of the tyrosine residues lead to loss of function. Therefore, the rejection is maintained for the claims indicated [see discussion as well].

10. No claim is allowed.

11. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP

□ 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for response to this final action is set to expire THREE MONTHS from the date of this action. In the event a first response is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event will the statutory period for response expire later than SIX MONTHS from the date of this final action.

12.

Abstract

*This application does not contain an abstract of the disclosure as required by 37 CFR 1.72(b). An abstract on a separate sheet is required.

*The abstract should be in narrative form and generally limited to a single paragraph within the range of 50 to 150 words [in length since the space provided for

Art Unit: 1652

the abstract on the computer tape by the printer is limited]. The form and legal phraseology often used in patent claims, such as "means" and "said", should be avoided in the abstract. The abstract should sufficiently describe the disclosure to assist readers in deciding whether there is a need for consulting the full patent text for details. MPEP 608.01(b).

13.

Sequence Rules

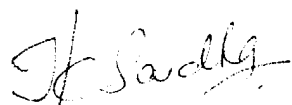
The instant specification [see drawings - Figures 15A-B; 16A-C, for example], present amino acid/nucleic acid sequences that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2), but fails to comply with the requirements. According to 37 CFR 1.821-825, every disclosed amino acid sequence of four or more residues or 10 or more nucleotides must be identified by a SEQ ID NO. The amino acid sequences presented in Figures 15A-B; 16A-C, for example [please check the entire specification] do not have SEQ ID NOs. In order to comply with the sequence rules Applicants must identify these sequences by providing SEQ ID NO :, and where required provide a new version of the sequence listing and disk.

If the sequences are already present in the sequence listing, the figure legend may be amended to indicate the appropriate SEQ ID NO: .

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Tekchand Saidha (Ph.D.) whose telephone number is (571) 272-0940. The examiner can normally be reached on Monday-Friday from 8:15 am to 4:45 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapu Achutamurthy, can be reached at (571) 272-0928. The fax phone number for this Group in the Technology Center is 703 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is 571 272-1600.



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March 24, 2004